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Statin Use and Reduced Risk of Biliary Tract Cancers in the United Kingdom

Clinical Practice Research Datalink

Zhiwei Liu^{1*}, Rotana Alsaggaf¹, Katherine A. McGlynn¹, Lesley Anderson², Huei-Ting Tsai^{3,4}, Bin Zhu¹, Yue Zhu⁵, Sam M. Mbulaiteye¹, Shahinaz M. Gadalla¹, Jill Koshiol¹

Short title: Statin Use and Risk of Biliary Tract Cancers

Author Affiliations:

1. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA
2. Centre for Public Health, School of Medicine, Dentistry and Biomedical Science, Queen's University Belfast, United Kingdom
3. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA
4. Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Georgetown University, Washington D.C., USA
5. Department of Epidemiology & Biostatistics, Milken Institute School of Public Health, The George Washington University, Washington DC, USA

Corresponding author:

Zhiwei Liu, Ph.D., Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Bethesda, MD 20850. Phone: 240-276-6726; Fax: 240-276-7806, email address: zhiwei.liu@nih.gov

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Author contributions to manuscript

ZL was involved in the study design, analysis and interpretation of the data, and writing the manuscript. RA, KAM, LA, HTT, YZ, SMM, and SMG were involved in conception of the study, interpretation of the data, and revision of the manuscript. BZ was involved in data analysis, interpretation of the data and revision of the manuscript. JK was involved in conception of the study, study design, interpretation of the data, and writing the manuscript. All authors revised the article critically for important intellectual content and gave final approval of the version to be published.

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Abbreviations: AVC, ampulla of Vater cancer; BMI, body mass index; BTC, Biliary tract cancer; CI, confidence interval; CPRD, Clinical Practice Research Datalink; GBC, gallbladder cancer; Q, quartile; OR, odds ratios

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Abstract

Objective: To evaluate the association between statin use and risk of biliary tract cancers (BTCs).

Design: This is a nested case-control study based on the United Kingdom Clinical Practice Research Datalink (CPRD). We included cases diagnosed with incident primary BTCs, including cancers of the gallbladder, bile duct (i.e., both intrahepatic and extrahepatic cholangiocarcinoma), ampulla of Vater, and mixed type, between 1990 and 2017. For each case, we selected five controls who did not develop BTCs at the time of case diagnosis, matched by sex, year of birth, calendar time, and years of enrollment in the general practice using incidence density sampling. A history of prescribed medications 1 year prior to diagnosis/selection was obtained from the patient prescription records. Odds ratios (ORs) and 95% confidence intervals (CIs) for associations between statins and BTC overall and by subtypes were estimated using conditional logistic regression, adjusted for relevant confounders.

Results: We included 3,118 BTC cases and 15,519 cancer-free controls. Current statin use versus non-use was associated with a reduced risk of all BTCs combined (adjusted OR=0.88, 95%CI: 0.79-0.98). The reduced risks were most pronounced among long-term users, as indicated by increasing number of prescriptions ($P_{\text{trend}} = 0.016$) and cumulative dose of statins ($P_{\text{trend}} = 0.008$). The magnitude of association was similar for statin use and risk of individual types of BTCs. The reduced risk of BTCs associated with current statin use versus non-use was more pronounced among persons with diabetes (adjusted OR=0.72, 95%CI: 0.57-0.91). Among non-diabetics, the adjusted OR for current statin use versus non-use was 0.91 (95%CI: 0.81-1.03, $P_{\text{heterogeneity}}=0.007$).

Conclusion: We provide evidence that current, but not former, statin use was associated with a lower risk of BTCs compared with nonuse of statins. If replicated, particularly in countries with a high incidence of BTCs, our findings could pave the way for evaluating the value of statins for BTC chemoprevention.

Key words: ampulla of Vater cancer, biliary tract cancer, cholangiocarcinoma, CPRD, gallbladder cancer, statin

Short summary

1. What is already known about this subject?

- Statins are commonly used cholesterol-lowering medications that have demonstrated effectiveness in the primary and secondary prevention of cardiovascular disease.
- Several epidemiological studies have shown that statins are associated with a lower risk of gallstone disease (gallstones or a history of cholecystectomy), but associations with biliary tract cancers (BTCs) have not been well studied.

2. What are the new findings?

- There was significantly reduced risk of biliary tract cancers among current users of statins, as compared with non-users (odds ratio, 0.88).
- The reduced risks were most pronounced among long-term users, as indicated by increasing number of prescriptions (P for trend = 0.016) and cumulative dose of statins (P for trend = 0.008).

3. How might it impact on clinical practice in the foreseeable future?

- Current or long-term statin use may reduce risk of biliary tract cancers.

- If replicated in other settings, the value of statins for BTC chemoprevention should be evaluated.

Introduction

Biliary tract cancers (BTCs) are comprised of cancers of the gallbladder, bile duct (*i.e.*, both intrahepatic and extrahepatic cholangiocarcinoma), and ampulla of Vater. BTCs are rare but highly fatal diseases, with a median overall survival of ~12 months.[1] Although the etiology of BTCs is largely unknown, the epidemiologic and molecular characteristics suggest that they are distinct disease entities.[1, 2] For example, gallbladder cancer (GBC) is more common in women than men, while other BTCs are more common in men.[3] Similarly, cirrhosis and infection with hepatitis B and C viruses are associated with intrahepatic cholangiocarcinoma, while their associations with GBC and ampulla of Vater cancer (AVC) are less clear.[1, 4]

Despite these differences, BTCs share common risk factors. For example, disorder of lipid regulation (*i.e.*, hyperlipidemia) has been associated with an increased risk of cancer at all sites in the biliary tract.[5] Hyperlipidemia is thought to interact with inflammation and pro-inflammatory immune response to influence the risk of BTCs.[6, 7] For GBC, local inflammation due to gallstones plays a central role,[8] while for cholangiocarcinoma, both intrahepatic and extrahepatic sclerosing cholangitis play a major role.[1] Inflammation from biliary adenomas, which are seen in patients with familial adenomatous polyposis,[9] is thought to contribute to the 100-fold higher risk of AVC in that population.[10] Finally, other causes of inflammation, such as bacterial infection and obesity/metabolic syndrome, may play a role in the etiology of BTC.[1]

Given these strong ties with dyslipidemia and inflammation, statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) could potentially reduce the risk

of BTCs. Statins are commonly used cholesterol-lowering medications that have demonstrated effectiveness in the primary and secondary prevention of cardiovascular disease.[11] Several studies have shown that statins are associated with a lower risk of gallstone disease (gallstones or a history of cholecystectomy) [12, 13, 14, 15], but associations with BTCs have not been well studied. To further our understanding of the associations between statins and BTCs, we thus conducted a nested case-control study within a large database of primary care electronic medical records – the United Kingdom (UK) Clinical Practice Research Datalink (CPRD).[16]

Methods

This study is based on data from the CPRD obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the national health service (NHS) as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. The study was approved by the Independent Scientific Advisory Committee of the CPRD (proposal#17_160.R).

Study Population and Design

The UK CPRD was established in 1987 and contains information on ~8.5% (13.3 million) of the UK population. All data are provided by general practitioners; the CPRD population is representative of the general UK population.[17] Detailed information includes demographic data, physician contacts, tests conducted, and medications prescribed. Diagnoses, physical findings, symptoms, and administrative events, such as referrals to specialists, are recorded using Read codes, the standard clinical terminology system used in general practice in the UK.[18]

In this nested case-control study, we included all persons whose most recent active registration at a CPRD practice overlapped with the study period from 1990 (three years after the establishment of the database) through 2017. Entry date was defined as the patient's current registration date (i.e., the later of the practice's up-to-standard date), and exit date was defined as the date of cancer diagnosis/selection, death, leaving the practice, or last collection of data from the practices, whichever occurred first. Eligible cases included persons aged 21-100 years with a first cancer diagnosis (except non-melanoma skin cancer) of BTC (Read codes provided in **Supplementary Table 1**) identified in CPRD during 1990-2017. To ascertain statin use, we excluded the 1-year period prior to cancer diagnosis to minimize the possibility of reverse causation (i.e., incipient cancer leading to statin use); therefore, the index date was defined as the date of BTC diagnosis minus one year. All cases were required to have at least one year of recorded activity in the CPRD prior to the index date (i.e., two years total of enrollment were required).

Five controls per case were randomly selected using incidence density sampling. Controls were individually matched on sex, year of birth (± 3 years), index year (± 3 years), and number of years in the general practice and in the CPRD prior to index date. All controls were required to be alive and cancer-free (except for non-melanoma skin cancer) prior to the diagnosis date of the matched case and were required to have at least one year of enrollment in the CPRD participating practice prior to the case index date (i.e., the date of BTC diagnosis minus one year; thus, two years total of enrollment were required). Selected controls with exit date before entry were excluded (N=55).

Ascertainment of Statins and Covariates

A history of prescribed medications prior to the index date was obtained from the patient prescription records. Drugs of interest included statins, other lipid-lowering agents (*i.e.*, bile acid sequestrant, cholesterol absorption inhibitor, fibrate, nicotinic acid derivative, Omega-3 fatty acid, and Bis-phenol antioxidant), treatment for type 2 diabetes (*i.e.*, metformin, insulin, Acetohexamide, Tolbutamide, Chlorpropamide, Glibenclamide, Glibornuride, Gliclazide, Rosiglitazone, Tolazamide, and Tolbutamide), aspirin, and cortisone, which were included because of their potential effect on metabolism. Statin use was defined as having two or more statin prescriptions recorded, and nonuse of statins was defined as having 0-1 prescriptions.[19] Former statin use was defined as use ending more than one year prior to the index date. Use ending within one year prior to the index date was considered as current use. Based on the distribution among controls, statin use was classified by time since first recorded statin use (0-2, 3-5, 6-8, and 9+ years), number of prescriptions (2-15, 16-35, 36-65, and 66+, representing approximate duration of use) and cumulative dose (quartiles), which was defined as number of pills multiplied by the dose per pill. This grouping strategy permitted examination of the trend for the association of increasing statin use with risk for BTCs. Finally, specific commonly used statins (atorvastatin, simvastatin, pravastatin, and rosuvastatin) were examined individually.

Because body mass index (BMI), smoking, alcohol drinking, diabetes mellitus, gallstones, cirrhosis, hepatitis virus infection, chronic heart disease, and dyslipidemia may be associated with both statin use and BTCs or BTCs at specific subsites, we identified persons who had these conditions prior to the index date. We also assessed healthy user effect, healthy adherer effect, and functional status prior to the index date because these factors have been suggested as important confounders in observational studies (**Supplementary Materials**).[20]

Statistical analyses

We used conditional logistic regression to estimate odds ratios (ORs) for the association of statins with BTCs overall and with individual types (*i.e.*, GBC, cholangiocarcinoma, and AVC). The regression model included adjustment for known BTC risk factors: BMI, smoking status, alcohol drinking status, and a history of diabetes.[21] GBC-specific analyses excluded 177 controls with a history of cholecystectomy because those controls were not at risk for developing GBC, and history of gallstones was additionally included in the model. Cholangiocarcinoma-specific analyses additionally included history of cirrhosis in the model.

Other potential confounders were selected if they changed the adjusted OR for BTC and statin use status by more than 10%. We first considered a fully adjusted model that included all potential confounders: a history of hepatitis virus infection, chronic heart disease, dyslipidemia, high exercise, healthy diet, cancer screening, influenza vaccination, pneumonia, dementia, comorbidity, and use of treatment for type 2 diabetes, aspirin, cortisone, or other lipid-lowering agents. However, additional adjustment for those variables resulted in only marginal changes in the ORs (**Supplementary Table 2**); such adjustments were therefore not included in the final model. We also selected covariates by mutually entering all potential confounders into a stepwise logistic regression model, with $P < 0.15$ as the model entry criterion and $P < 0.05$ for a variable to remain in the model. Likewise, adjustment for variables selected resulted in OR changes of less than 10% (**Supplementary Table 2**). We thus only present results from the minimally adjusted model. We tested for linear trends across statin use categories with the Wald test using categorical values of the number of prescriptions and cumulative dose with 1 degree of freedom.

We evaluated potential effect modification by matching variables (*i.e.*, sex, age at index date [≤ 70 versus > 70 years; the age cutoff was chosen to create two equally large age groups

among the control subjects, among whom the median age was 72 years], and index year [≤ 2004 versus >2004 because 10 mg of simvastatin became available over-the-counter in August 2004] [22]). Likelihood ratio tests were used to compare models with and without an interaction term between statin use and each potential modifier. Because statin use has been associated with increased risk of diabetes,[23, 24, 25] we conducted a joint analysis of diabetes and statin use initiated before or after diabetes diagnosis. We used patients with diabetes who did not use statins as the reference group for a model focused on the potential protective effect of statins on BTCs among patients with diabetes; this model was additionally adjusted for treatment for type 2 diabetes. We then reran the model using non-diabetic patients who did not use statins as the reference group to focus on the effect of former or current statin use among non-diabetics.

In sensitivity analyses, we focused on incident statin users (defined as those with the first recorded use of statins of ≥ 5 years after entry into CPRD) to limit the effect of confounding (*i.e.*, intended and unintended treatment effects) and yield results closer to those that would be seen in randomized clinical controlled trial.[26] We also conducted analyses excluding 145 cases with carcinoma in situ of the biliary system and their matched controls, excluding subjects with non-biliary cancer in situ (*i.e.*, all carcinoma in situ except that of the biliary system) since diagnosis of in situ cancer may have led to lifestyle changes, or excluding subjects with missing/unknown information on smoking, alcohol drinking, and BMI. Finally, although information on treatment is not complete in the CPRD because this information is reported by primary care physicians only, not specialists, cases with supporting clinical codes that indicated presence of BTCs such as diagnostic exams (biopsies), treatment (chemotherapy, radiotherapy, surgery), palliative care, and referrals to specialty care were considered as confirmed BTCs.

Statistical analyses were performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the distribution of demographic characteristics and other potential risk factors. A total of 3,118 BTC cases (708 GBC, 1678 cholangiocarcinoma, 228 AVC, 500 mixed, 4 unknown) and 15,519 cancer-free controls were included (**Table 1**). By design, cases and controls were individually-matched on sex, age, index year, and years in the CPRD participating practice prior to the index date. Cases were more likely to be obese; be current smokers; drink alcohol; have a history of chronic diseases, including diabetes, gallstones, and cirrhosis; be infected with hepatitis viruses; have treatment for type 2 diabetes; and use aspirin or cortisone. Controls were more likely to be diagnosed with dementia.

Table 2 shows adjusted ORs for statin use and risk of all BTCs combined. Although former statin use was not associated with BTC risk, current use versus non-use was associated with a reduced risk of BTCs (adjusted OR=0.88, 95%CI: 0.79-0.98, **Table 2**). Individuals who started using statins nine or more years before the index date had reduced risk of BTCs (OR=0.85, 95%CI: 0.72-1.01), but the trend was not consistent across increasing categories of time since first statin use ($P_{\text{trend}}=0.128$). Although there was some evidence of a dose-response trend with increasing number of prescriptions ($P_{\text{trend}}=0.016$) and cumulative dose of statins ($P_{\text{trend}}=0.008$), the trend was not consistent across all categories, and only the highest quartile (Q4) compared with nonuse of statins was statistically significant. For example, compared with nonuse of statins, the adjusted OR of the highest quartile (Q4) for cumulative dose was 0.81

(95%CI: 0.68-0.96). We did not observe heterogeneity by type of statin but had limited statistical power for individual types of statins (**Supplementary Table 3**).

The reduced risk associated with statin use was similar for individual types of BTCs (**Table 3**). For example, the adjusted ORs for current statin use versus nonuse and risk of GBC, cholangiocarcinoma, and AVC were 0.86 (95%CI: 0.67-1.09), 0.87 (0.75-1.01), and 0.89 (0.59-1.34), respectively. There were no clear dose-response relationships between risk of individual types of BTCs and number of prescriptions and cumulative dose, but the ORs were of similar magnitude to those for BTCs overall.

The observed associations were similar for men and women, for individuals ≤ 70 and >70 years of age at index date, and for those with an index year of ≤ 2004 and >2004 (all $P_{\text{heterogeneity}} > 0.05$, **Supplementary Table 4**). In the joint analysis by history of diabetes, we found that statin use was associated with a lower risk of BTCs among patients with diabetes, with an adjusted OR for current statin use versus non-use of 0.72 (95%CI: 0.57-0.91). Among non-diabetics, the adjusted OR for current statin use versus non-use was 0.91 (95%CI: 0.81-1.03, $P_{\text{heterogeneity}} = 0.007$). The reduced risk of BTCs was more pronounced among participants with statins prescribed before diabetes was diagnosed (adjusted OR=0.59, 95%CI: 0.44-0.81) than among those with statins prescribed after diabetes was diagnosed (0.84 [0.66-1.08], $P_{\text{heterogeneity}} = 0.03$).

In sensitivity analyses, the adjusted ORs remained stable in patients with incident current statin use (OR=0.81, 95%CI: 0.70-0.94), excluding persons with biliary carcinoma in situ and their controls (OR for current statin use=0.88, 95%CI: 0.79-0.98), and among cases and controls without a history of cancer in situ except carcinoma in situ of biliary system (0.89, 95%CI: 0.79-

0.99) or without missing/unknown status for smoking, alcohol drinking, and BMI (0.90, 95%CI: 0.80-1.02).

Discussion

In this large study, we observed a reduced risk of BTCs among current statin users compared to nonusers. Reduced risk of BTCs was also more pronounced among subjects with the highest number of prescriptions and cumulative dose of statins, suggesting that long-term statin users may have a lower risk of developing BTCs. The risk estimate was consistent across individual types of BTCs, age groups, sex, and calendar time. Adjustment for various risk factors did not substantively alter the results. Finally, we also observed a risk reduction among persons with diabetes. If replicated in other studies, these findings suggest that statins may have a role as chemopreventive agents.

Comparison to other studies

To our knowledge, this study is the first to address the association between statin use and risk of cancer across the biliary tract. Our findings are in line with the one previous study focusing on one individual type of BTC (cholangiocarcinoma) in Taiwan, which reported that the adjusted OR for statin use versus nonuse for cholangiocarcinoma was 0.80 (95%CI: 0.71-0.90).[27] The results are also consistent with studies that have demonstrated a decreased risk of gallstone disease,[12, 13, 14, 15] a risk factor for BTCs,[28] especially GBC.[1, 2] Statins could potentially reduce risk of BTCs through suppression of biliary cholesterol secretion and saturation and anti-inflammatory and endothelial effects.[29, 30] The reduction in hepatic and gallbladder bile cholesterol concentrations could alter bile acid composition and interfere with gallstone production or even promote gallstone dissolution.[31] In addition, both experimental

and clinical studies provide evidence that statins have anti-inflammatory effects.[29, 30] Statins reduce circulating C-reactive protein and pro-inflammatory cytokines and chemokines.[32, 33] Statins also favorably affect important pathways regulating nitric oxide bioavailability, which is critical for maintaining endothelium homeostasis via statins' vasodilatory, anti-inflammatory, and overall anti-atherogenic effects. In addition, statins have been shown to regulate expression of many inflammatory genes.[30] Associations between statin use and lower risk of cancers related to inflammation, including cancers of the colorectum [34, 35] and esophagus [36, 37, 38], have been reported in epidemiological studies. However, we did not observe a joint effect of use of both statins and aspirin (data not shown), as has been reported for cancer of the esophagus [37, 38].

Our findings of reduced BTC risk among persons with diabetes using statins should be interpreted with caution. Some studies suggest that statins may increase the risk of diabetes, although results are inconsistent.[23, 24] Experimental data support the hypothesis that statins may cause diabetes by altering glucose homeostasis through both impaired insulin secretion and diminished insulin sensitivity.[39] Following this hypothesis, statins could increase the risk of BTCs by increasing risk of diabetes. However, in the present study, we observed a reduced risk of BTCs among persons with diabetes who used statins before their diabetes was diagnosed, as compared with those with diabetes who did not use statins. Lipophilic (simvastatin and atorvastatin) and hydrophilic (pravastatin and rosuvastatin) statins have been observed to have different diabetogenic effects,[40] but we lacked the power to investigate whether the observed reduced risk of BTCs was driven by specific types of statins. Additional studies are needed to clarify the associations between statins, diabetes, and BTCs, but overall our results suggest that statins reduce the risk of BTCs both in patients with diabetes and those without.

Our study has several strengths. First, it was conducted using a large, well-established, validated, longitudinal primary-care database with long-term follow-up. This database is known for accuracy of diagnoses, including cancer, and completeness of pharmacy data.[41, 42] Second, all information on diseases and drug exposures in the CPRD is recorded prior to BTC diagnosis and in the absence of a study hypothesis, reducing the risk of recall bias. Third, we could evaluate the impact of various important confounders (BMI, smoking, alcohol drinking, a history of diabetes, hepatitis virus infection, chronic heart disease, dyslipidemia, and use of treatment for type 2 diabetes, aspirin, cortisone, or other lipid-lowering agents); such information is usually not accessible in registry-based studies. Although we did not adjust for socioeconomic status (SES), SES has been not associated with statin prescribing in England.[43] In addition, cases and controls were matched on general practice, and the universal health care coverage in the UK may, to some degree, control for SES. Finally, we conducted a large number of sensitivity analyses that further support the robustness of our findings.

Our study has a few limitations. First, although our sample size was sufficient for all BTCs combined, power was limited for individual types of BTCs and individual statins. Second, compliance rates among persons taking statins could not be evaluated, leading to potential exposure misclassification. Third, although we adjusted for several factors, these conditions could be incompletely captured in the database; residual confounding is possible even after our adjustment. For example, our adjustment for confounding by healthy user effect, healthy adherer effect, and functional status or cognitive impairment, which are not usually considered in observational studies,[20] did not change the magnitude of the association between statin use and risk of BTCs. Fourth, although previous validation studies have reported that cancer diagnoses are accurate and complete,[41, 44] the diagnosis of BTCs in the present study was not verified

and misclassification cannot be ruled out. Further studies conducted in databases with validated cancer diagnosis are warranted. Fifth, use of statins may not be completely captured after 2004 because 10mg simvastatin became available over-the-counter at that time, and a previous study showed a decreased trend in statin prescribing since 2004.[22] We conducted a stratified analysis by calendar year but did not observe significant heterogeneity in the association before and after 2004. It is also likely that this misclassification occurs equally for cases and controls and thus is nondifferential by case-control status. If true, this misclassification could underestimate the strength of the reduced risk of BTCs associated with use of statins. Finally, we cannot rule out a potential role of chance given the number of tests evaluated with the potential for false positives.

In conclusion, this large observational study provides evidence that current or long-term statin use is associated with decreased risk of BTCs. Our findings should be replicated in other populations, particularly in high-risk areas, such as Chile, to confirm our observations and further establish the potential value of statins for BTC chemoprevention.

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Table 1. Characteristics of cases with biliary tract cancer and controls, CPRD ^a

Characteristic	Case (n=3,118)	Control (n=15,519)	P value
Cancer site (n, %)			--
Gallbladder	708 (22.7)	--	
Bile duct	1678 (53.8)	--	
Ampulla of Vater	228 (7.3)	--	
Mixed	500 (16.0)	--	
Missing	4 (0.1)	--	
Index year (n, %)			
1989-1999	369 (11.8)	1836 (11.8)	--
2000-2004	633 (20.3)	3149 (20.3)	
2005-2009	884 (28.4)	4422 (28.5)	
2010-2016	1232 (39.5)	6112 (39.4)	
Years in CPRD prior to index date			
Mean ± SD	22.4 ± 17.0	22.6 ± 17.0	--
Age at index date, years (n, %)			
20-49	525 (16.8)	2607 (16.8)	--
50-69	756 (24.2)	3822 (24.6)	
70-79	1010 (32.4)	5026 (32.4)	
80-99	827 (26.5)	4064 (26.2)	
Mean ± SD	71.0 (11.9)	71.0 (11.8)	
Sex (n, %)			--
Male	1439 (46.2)	7156 (46.1)	--
Female	1679 (53.8)	8363 (53.9)	
Body mass index, kg/m² (n, %)			
<18.5 (low)	28 (0.9)	168 (1.1)	<0.001
18.5–24.9 (normal)	853 (27.4)	4788 (30.9)	
25.0–29.9 (overweight)	1102 (35.3)	5120 (33.0)	
30.0+ (obese)	650 (20.8)	2577 (16.6)	
Missing/Unknown	485 (15.6)	2866 (18.5)	
Smoking status (n, %)			
Never	618 (19.8)	3472 (22.4)	<0.001
Former	1484 (47.6)	7340 (47.3)	
Current	764 (24.5)	2964 (19.1)	
Missing/Unknown	252 (8.1)	1743 (11.2)	
Alcohol drinking status (n, %)			
Never	458 (14.7)	2339 (15.1)	0.002
Former	131 (4.2)	548 (3.5)	
Current	2022 (64.8)	9709 (62.6)	

Missing/Unknown	507 (16.3)	2923 (18.8)	
Chronic disease history (n, %)			
Diabetes	15 (0.5)	11 (0.1)	<0.001
Gallstone	29 (0.9)	34 (0.2)	<0.001
Cirrhosis	234 (7.5)	480 (3.1)	<0.001
Hepatitis virus infection	127 (5.3)	546 (4.5)	0.138
Cholecystectomy ^b	677 (21.7)	3171 (20.4)	0.113
Chronic heart disease	481 (15.4)	2540 (16.4)	0.203
Dyslipidemia	458 (14.7)	1648 (10.6)	<0.001
Prescription drug use history (n, %)			
Treatment for Type 2 diabetes	330 (10.6)	1234 (8.0)	<0.001
Aspirin	1070 (34.3)	4927 (31.7)	0.002
Cortisone	925 (29.7)	4032 (26.0)	<0.001
Other lipid-lowering agents	134 (4.3)	594 (3.8)	0.236
Healthy user effect (n, %)			
High exercise	26 (0.8)	186 (1.2)	0.097
Healthy diet	633 (20.3)	2989 (19.3)	0.188
Healthy adherer effect (n, %)			
Cancer screening	672 (21.6)	3152 (20.3)	0.123
Influenza vaccination	398 (12.8)	1916 (12.3)	0.537
Functional status or cognitive impairment (n, %)			
Pneumonia	101 (3.2)	500 (3.2)	1.000
Dementia	33 (1.1)	336 (2.2)	<0.001
Comorbidity	155 (5.0)	673 (4.3)	0.128

a Excludes 55 controls with entry date after exit date.

b Excludes 708 cases with gallbladder cancer and their 3,508 matched controls.

Table 2. Association between statin use and biliary tract cancers, CPRD

Characteristic	Case (n=3,118)	Control (n=15,519)	Adjusted OR (95% CI) ^a
Any statin use			
Nonusers	2159 (69.2)	10934 (70.5)	ref.
Ever	959 (30.8)	4585 (29.5)	0.92 (0.83, 1.02)
Former ^b	199 (6.4)	831 (5.4)	1.10 (0.92, 1.31)
Current	760 (24.4)	3754 (24.2)	0.88 (0.79, 0.98)
Time since first statin use recorded (years)			
Nonusers	2159 (69.2)	10934 (70.5)	ref.
0-2	206 (6.6)	1064 (6.9)	0.87 (0.74, 1.02)
3-5	292 (9.4)	1316 (8.5)	0.98 (0.84, 1.13)
6-8	233 (7.5)	1060 (6.8)	0.97 (0.82, 1.14)
9+	228 (7.3)	1145 (7.4)	0.85 (0.72, 1.01)
<i>P</i> trend			0.128
No. of prescriptions			
Nonusers	2159 (69.2)	10934 (70.5)	ref.
2-15	254 (8.1)	1169 (7.5)	0.98 (0.84, 1.14)
16-35	236 (7.6)	1144 (7.4)	0.92 (0.79, 1.08)
36-65	252 (8.1)	1089 (7.0)	1.00 (0.85, 1.17)
66+	217 (7.0)	1183 (7.6)	0.76 (0.64, 0.91)
<i>P</i> trend			0.016
Cumulative dose ^c			
Nonusers	2159 (69.2)	10934 (70.5)	ref.
Q1	269 (8.6)	1146 (7.4)	1.07 (0.93, 1.24)
Q2	225 (7.2)	1147 (7.4)	0.85 (0.73, 1.00)
Q3	242 (7.8)	1147 (7.4)	0.90 (0.77, 1.06)
Q4	223 (7.2)	1144 (7.4)	0.81 (0.68, 0.96)
Missing	0	1	
<i>P</i> trend			0.008

Abbreviation: CI, confidence interval; Q, quartile; OR, odds ratios

^a Adjusted for body mass index, smoking, alcohol drinking, and diabetes

^b Former: Stopped using statins 1+ years before index date

^c Q1=13175, Q2=32480, Q3=65520

Table 3. Association between statin use and subsites of biliary tract cancer, CPRD ^a

Characteristic	Gallbladder ^b			Bile duct ^c			Ampulla of Vater		
	Case (n=708)	Control (n=3331)	Adjusted OR (95% CI)	Case (n=1678)	Control (n=8322)	Adjusted OR (95% CI)	Case (n=228)	Control (n=1125)	Adjusted OR (95% CI) ^a
Any statin use									
Nonusers	495 (69.9)	2374 (71.3)	ref.	1167 (69.5)	5880 (70.7)	ref.	162 (71.1)	802 (71.3)	ref.
Ever	213 (30.1)	957 (28.7)	0.89 (0.71, 1.11)	511 (30.5)	2442 (29.3)	0.92 (0.80, 1.05)	66 (28.9)	323 (28.7)	0.96 (0.66, 1.41)
Former	49 (6.9)	198 (5.9)	1.01 (0.69, 1.48)	106 (6.3)	426 (5.1)	1.14 (0.89, 1.45)	17 (7.5)	65 (5.8)	1.30 (0.68, 2.46)
Current	164 (23.2)	759 (22.8)	0.86 (0.67, 1.09)	405 (24.1)	2016 (24.2)	0.87 (0.75, 1.01)	49 (21.5)	258 (22.9)	0.89 (0.59, 1.34)
Time since first statin use recorded (years)									
Nonusers	495 (69.9)	2374 (71.3)	ref.	1167 (69.5)	5880 (70.7)	ref.	162 (71.1)	802 (71.3)	ref.
0-2	41 (5.8)	195 (5.9)	0.84 (0.57, 1.24)	110 (6.6)	572 (6.9)	0.82 (0.66, 1.04)	14 (6.1)	82 (7.3)	0.74 (0.39, 1.41)
3-5	63 (8.9)	297 (8.9)	0.85 (0.61, 1.19)	160 (9.5)	691 (8.3)	1.02 (0.84, 1.25)	15 (6.6)	81 (7.2)	0.88 (0.47, 1.63)
6-8	60 (8.5)	228 (6.8)	1.08 (0.76, 1.54)	125 (7.4)	569 (6.8)	0.97 (0.78, 1.22)	14 (6.1)	82 (7.3)	0.86 (0.45, 1.65)
9+	49 (6.9)	237 (7.1)	0.79 (0.54, 1.17)	116 (6.9)	610 (7.3)	0.82 (0.65, 1.05)	23 (10.1)	78 (6.9)	1.68 (0.89, 3.15)
<i>P</i> trend			0.391			0.246			0.433
No. of prescriptions									
Nonusers	495 (69.9)	2374 (71.3)	ref.	1167 (69.5)	5880 (70.7)	ref.	162 (71.1)	802 (71.3)	ref.
2-15	54 (7.6)	227 (6.8)	0.98 (0.69, 1.39)	136 (8.1)	642 (7.7)	0.93 (0.76, 1.15)	19 (8.3)	83 (7.4)	1.02 (0.58, 1.81)
16-35	47 (6.6)	248 (7.4)	0.76 (0.53, 1.09)	133 (7.9)	608 (7.3)	0.97 (0.79, 1.20)	18 (7.9)	71 (6.3)	1.20 (0.66, 2.15)
36-65	60 (8.5)	242 (7.3)	0.97 (0.69, 1.36)	136 (8.1)	568 (6.8)	1.04 (0.83, 1.29)	14 (6.1)	81 (7.2)	0.80 (0.42, 1.54)
66+	52 (7.3)	240 (7.2)	0.84 (0.58, 1.24)	106 (6.3)	624 (7.5)	0.71 (0.55, 0.90)	15 (6.6)	88 (7.8)	0.77 (0.39, 1.50)
<i>P</i> trend			0.306			0.063			0.498
Cumulative dose ^d									
Nonusers	495 (69.9)	2374 (71.3)	ref.	1167 (69.5)	5880 (70.7)	ref.	162 (71.1)	802 (71.3)	ref.
Q1	62 (8.8)	240 (7.2)	1.08 (0.78, 1.49)	145 (8.6)	635 (7.6)	1.02 (0.83, 1.25)	15 (6.6)	77 (6.8)	0.92 (0.51, 1.65)
Q2	52 (7.3)	239 (7.2)	0.88 (0.62, 1.25)	114 (6.8)	598 (7.2)	0.83 (0.66, 1.04)	22 (9.6)	81 (7.2)	1.30 (0.74, 2.31)
Q3	44 (6.2)	239 (7.2)	0.66 (0.45, 0.97)	139 (8.3)	601 (7.2)	1.00 (0.81, 1.24)	10 (4.4)	82 (7.3)	0.67 (0.33, 1.36)

Q4	55 (7.8)	238 (7.1)	0.91 (0.62, 1.32)	113 (6.7)	608 (7.3)	0.79 (0.62, 1.00)	19 (8.3)	83 (7.4)	0.97 (0.51, 1.85)
<i>P</i> trend			0.141			0.081			0.739

Abbreviation: CI, confidence interval; Q, quartile; OR, odds ratio

a ORs are adjusted for body mass index, smoking, alcohol drinking, and diabetes.

b ORs are additionally adjusted for gallstones. Excludes 177 controls with a history of cholecystectomy.

c ORs are additionally adjusted for cirrhosis.

d For gallbladder cancer, Q1=14560, Q2= 34720, Q3= 66080; for cancer in Bile duct, Q1= 13440, Q2= 32480, Q3= 66080; for cancer of Ampulla of Vater, Q1= 12320, Q2=33600, Q3=63840.

Supplementary Materials

Identification of indicators of healthy user effect, healthy adherer effect, and functional status

We assessed healthy user effect, healthy adherer effect, and functional status prior to the index date because these factors have been suggested as important confounders in observational studies.[1] We used high exercise (*i.e.*, Readcodes for active/intermediate/heavy exercise or exercises ≥ 1 time per work) and healthy diet (*i.e.*, Readcodes for healthy diet, vegetarian diet, low cholesterol diet, gluten free diet, high fiber diet, low fat diet, or low salt diet) as indications of healthy users, participation in cancer screening and influenza vaccination as indications of healthy adherers, and pneumonia, dementia, and certain comorbidities (*i.e.*, organ failure including respiratory system, heart, liver, and kidney) as indications of functional status.

Reference

- 1 Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med 2011;**26**:546-50.

Supplementary Table 1. Read codes used to identify biliary tract cancers, CPRD

Cancer site	medcode	readcode	readterm
Gallbladder cancer			
	16105	B160.00	Malignant neoplasm of gallbladder
	31393	B160.11	Carcinoma gallbladder
	46594	B808300	Carcinoma in situ of gall bladder
Cholangiocarcinoma			
	8711	BB5D100	[M]Cholangiocarcinoma
	40438	BB5D111	[M]Bile duct carcinoma
	41313	BB5D300	[M]Bile duct cystadenocarcinoma
	110775	B151100	Malignant neoplasm of interlobular biliary canals
	89593	B151200	Malignant neoplasm of intrahepatic biliary passages
	16915	B151.00	Malignant neoplasm of intrahepatic bile ducts
	61643	B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
	99580	B808100	Carcinoma in situ of intrahepatic bile ducts
	58088	B151400	Malignant neoplasm of intrahepatic gall duct
	65124	B151000	Malignant neoplasm of interlobular bile ducts
	23433	B161.00	Malignant neoplasm of extrahepatic bile ducts
	74896	B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
	36495	B161211	Carcinoma common bile duct
	7982	B161200	Malignant neoplasm of common bile duct
	52537	B161100	Malignant neoplasm of hepatic duct
	37501	B808200	Carcinoma in situ of hepatic duct
	64089	B808500	Carcinoma in situ of common bile duct
	72445	B161000	Malignant neoplasm of cystic duct
Ampulla of Vater cancer			
	10949	B162.00	Malignant neoplasm of ampulla of Vater
	21792	B808600	Carcinoma in situ of ampulla of Vater
	105613	B161300	Malignant neoplasm of sphincter of Oddi
Mixed			
	54103	B16.00	Malignant neoplasm gallbladder and extrahepatic bile ducts
	15907	B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
	60312	B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
	38978	B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
	8918	B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
	35039	B163.00	Malignant neoplasm, overlapping lesion of biliary tract
	54103	B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
	70516	BB5D.11	[M]Biliary tract adenomas and adenocarcinomas
	107299	BB5D700	[M]Combined hepatocellular carcinoma and cholangiocarcinoma
	110147	BB5D711	[M]Hepatocholangiocarcinoma
	36031	BB5D.00	[M]Hepatobiliary tract adenomas and carcinomas

66673	B808.00	Carcinoma in situ of liver and biliary system
51934	B808.11	Carcinoma in situ of biliary system
98540	B808z00	Carcinoma in situ of liver or biliary system NOS

Supplementary Table 2. Association between statin use and biliary tract cancers, CPRD

Characteristic	Case (n=3,118)	Control (n=15,519)	Stepwise selection Adjusted OR (95% CI) ^a	Fully Adjusted OR (95% CI) ^b
Any statin use				
Nonusers	2159 (69.2)	10934 (70.5)	ref.	ref.
Ever	959 (30.8)	4585 (29.5)	0.92 (0.81, 1.03)	0.91 (0.81, 1.03)
Former ^c	199 (6.4)	831 (5.4)	1.07 (0.89, 1.29)	1.06 (0.88, 1.29)
Current	760 (24.4)	3754 (24.2)	0.88 (0.78, 1.00)	0.88 (0.78, 1.00)
Time since statin use firstly recorded (years)				
Nonusers	2159 (69.2)	10934 (70.5)	ref.	ref.
0-2	206 (6.6)	1064 (6.9)	0.86 (0.72, 1.02)	0.85 (0.72, 1.02)
3-5	292 (9.4)	1316 (8.5)	0.97 (0.83, 1.14)	0.96 (0.82, 1.13)
6-8	233 (7.5)	1060 (6.8)	0.97 (0.81, 1.16)	0.96 (0.80, 1.15)
9+	228 (7.3)	1145 (7.4)	0.87 (0.71, 1.05)	0.86 (0.70, 1.04)
<i>P</i> trend			0.266	0.232
No. of prescriptions				
Nonusers	2159 (69.2)	10934 (70.5)	ref.	ref.
2-15	254 (8.1)	1169 (7.5)	0.95 (0.81, 1.12)	0.94 (0.80, 1.11)
16-35	236 (7.6)	1144 (7.4)	0.91 (0.77, 1.08)	0.90 (0.76, 1.07)
36-65	252 (8.1)	1089 (7.0)	0.99 (0.83, 1.18)	0.98 (0.82, 1.17)
66+	217 (7.0)	1183 (7.6)	0.78 (0.64, 0.95)	0.77 (0.64, 0.94)
<i>P</i> trend			0.048	0.043
Cumulative dose ^d				
Nonusers	2159 (69.2)	10934 (70.5)	ref.	ref.
Q1	269 (8.6)	1146 (7.4)	1.05 (0.89, 1.23)	1.04 (0.88, 1.22)
Q2	225 (7.2)	1147 (7.4)	0.85 (0.71, 1.01)	0.84 (0.71, 1.01)
Q3	242 (7.8)	1147 (7.4)	0.89 (0.75, 1.06)	0.89 (0.75, 1.06)
Q4	223 (7.2)	1144 (7.4)	0.82 (0.67, 0.99)	0.81 (0.67, 0.98)
Missing	0	1		
<i>P</i> trend			0.017	0.015

Abbreviation: CI, confidence interval; Q, quartile; OR, odds ratios

^a Adjusted for BMI, smoking, alcohol drinking, hepatitis virus infection, cirrhosis, gallstone, dyslipidemia, diabetes, Aspirin, cortisone, high exercise, and dementia.

^b Adjusted for BMI, smoking, alcohol drinking, hepatitis virus infection, cirrhosis, gallstone, chronic heart disease, dyslipidemia, diabetes, Aspirin, cortisone, other lipid regulation drug, high exercise, health diet, pneumonia, cancer screening, influenza vaccination, dementia, and comorbidity.

^c Former: Stopped using statins 1+ years before index date

^d Q1=13175, Q2=32480, Q3=65520

Supplementary Table 3. Association between statin use and biliary tract cancers overall and by subtype, CPRD ^a

Characteristic	Biliary tract cancers overall			Gallbladder ^b			Bile duct			Ampulla of Vater		
	Case (n=3,118)	Control (n=15,519)	Adjusted OR (95% CI)	Case (n=708)	Control (n=3331)	Adjusted OR (95% CI)	Case (n=1678)	Control (n=8322)	Adjusted OR (95% CI)	Case (n=228)	Control (n=1125)	Adjusted OR (95% CI)
Type of statin												
Nonusers	2159 (69.2)	10934 (70.5)	ref.	171 (24.2)	763 (22.9)	ref.	408 (24.3)	1988 (23.9)	ref.	162 (71.1)	802 (71.3)	ref.
Simvastatin	764 (24.5)	3696 (23.8)	0.92 (0.83, 1.02)	77 (10.9)	384 (11.5)	0.89 (0.70, 1.12)	195 (11.6)	930 (11.2)	0.91 (0.79, 1.04)	52 (22.8)	258 (22.9)	0.93 (0.63, 1.39)
Atorvastatin	361 (11.6)	1789 (11.5)	0.88 (0.78, 1.01)	25 (3.5)	100 (3.0)	0.84 (0.63, 1.12)	57 (3.4)	321 (3.9)	0.94 (0.79, 1.13)	29 (12.7)	126 (11.2)	1.15 (0.70, 1.87)
Pravastatin	111 (3.6)	553 (3.6)	0.91 (0.74, 1.13)	16 (2.3)	59 (1.8)	1.01 (0.62, 1.65)	27 (1.6)	139 (1.7)	0.81 (0.60, 1.10)	10 (4.4)	33 (2.9)	1.64 (0.76, 3.54)
Rosuvastatin	57 (1.8)	260 (1.7)	0.98 (0.72, 1.33)	2 (0.3)	25 (0.8)	1.08 (0.57, 2.02)	13 (0.8)	69 (0.8)	0.87 (0.57, 1.33)	6 (2.6)	17 (1.5)	1.73 (0.65, 4.60)

Abbreviation: CI, confidence interval; OR, odds ratios

a Adjusted for body mass index, smoking, alcohol drinking, and diabetes.

b Odds ratios are additionally adjusted for gallstones. Excludes 177 controls with a history of cholecystectomy.

Supplementary Table 4. Association between statin use and biliary tract cancers, stratified by sex, age at index date and index year, CPRD a

Characteristic	Sex				Age at index date (years)						Index year							
	Male		Female		<i>P</i> heterogeneity		≤ 70		>70		<i>P</i> heterogeneity		≤2004		>2004		<i>P</i> heterogeneity	
	No. of cases/controls	Adjusted OR (95% CI)	No. of cases/controls	Adjusted OR (95% CI)			No. of cases/controls	Adjusted OR (95% CI)	No. of cases/controls	Adjusted OR (95% CI)			No. of cases/controls	Adjusted OR (95% CI)	No. of cases/controls	Adjusted OR (95% CI)		
Any statin use					0.3						0.345							0.953
Nonusers	929/4790	ref.	1230/6144	ref.			1085/5475	ref.	1074/5459	ref.			907/4521	ref.	1252/6413	ref.		
Former	98/364	1.34 (1.03, 1.74)	101/466	0.94 (0.74, 1.20)			53/229	1.03 (0.74, 1.42)	146/601	1.13 (0.91, 1.40)			10/57	0.79 (0.39, 1.59)	189/773	1.14 (0.94, 1.37)		
Current	412/2002	0.94 (0.81, 1.09)	348/1752	0.83 (0.71, 0.97)			254/1285	0.85 (0.71, 1.01)	506/2469	0.90 (0.79, 1.03)			85/406	0.86 (0.66, 1.12)	675/3348	0.89 (0.79, 1.00)		
No. of prescriptions					0.273						0.463							0.997
Nonusers	929/4790	ref.	1230/6144	ref.			1085/5475	ref.	1074/5459	ref.			907/4521	ref.	1252/6413	ref.		
2-15	134/581	1.09 (0.88, 1.35)	120/587	0.87 (0.70, 1.08)			91/469	0.85 (0.67, 1.09)	163/699	1.07 (0.88, 1.30)			47/227	0.86 (0.61, 1.21)	207/941	1.00 (0.84, 1.19)		
16-35	117/571	0.95 (0.76, 1.20)	119/573	0.89 (0.71, 1.11)			92/432	0.95 (0.74, 1.22)	144/712	0.90 (0.74, 1.11)			26/139	0.79 (0.51, 1.23)	210/1005	0.94 (0.79, 1.12)		
36-65	139/594	1.06 (0.85, 1.32)	113/495	0.94 (0.75, 1.19)			76/344	0.92 (0.70, 1.22)	176/745	1.03 (0.85, 1.26)			16/73	0.87 (0.49, 1.52)	236/1016	1.02 (0.86, 1.20)		
66+	120/620	0.85 (0.67, 1.08)	97/563	0.69 (0.53, 0.88)			48/269	0.73 (0.52, 1.04)	169/914	0.78 (0.63, 0.95)			6/24	1.08 (0.43, 2.71)	211/1159	0.77 (0.65, 0.92)		
<i>P</i> trend		0.433		0.012				0.112		0.065				0.339		0.039		
Cumulative dose					0.366						0.566							0.577
Nonusers	929/4790	ref.	1230/6144	ref.			1085/5475	ref.	1074/5459	ref.			907/4521	ref.	1252/6413	ref.		
Q1	133/553	1.15 (0.93, 1.43)	136/593	1.00 (0.81, 1.23)			90/420	0.98 (0.76, 1.25)	179/726	1.13 (0.94, 1.36)			61/279	0.93 (0.69, 1.26)	208/867	1.11 (0.94, 1.32)		
Q2	123/576	0.97 (0.78, 1.22)	102/571	0.75 (0.59, 0.95)			78/401	0.83 (0.63, 1.08)	147/746	0.87 (0.71, 1.07)			25/131	0.75 (0.48, 1.18)	200/1016	0.87 (0.73, 1.04)		
Q3	136/622	0.98 (0.78, 1.22)	106/525	0.83 (0.66, 1.05)			73/382	0.81 (0.61, 1.08)	169/765	0.95 (0.78, 1.16)			7/47	0.65 (0.29, 1.46)	235/1100	0.93 (0.79, 1.10)		
Q4	118/615	0.84 (0.66, 1.07)	105/529	0.79 (0.62, 1.02)			66/311	0.86 (0.63, 1.17)	157/833	0.79 (0.64, 0.98)			2/6	1.22 (0.24, 6.21)	221/1138	0.83 (0.69, 0.99)		
<i>P</i> trend		0.188		0.976				0.841		0.193				0.634		0.218		

Abbreviation: CI, confidence interval; OR, odds ratios

a Adjusted for body mass index smoking, alcohol drinking, and diabetes